VARIATIONAL APPROACH TO ENHANCED SAMPLING AND FREE ENERGY CALCULATIONS

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Many enhanced sampling methods are based on the introduction of a bias potential which is a function of a small number of collective variables (CVs) $\mathbf{s}$ and is designed to enhance transitions between the metastable states. However, constructing a such a bias is often not easy.

Here we introduce a variational principle [1] which shows that the bias $V(\mathbf{s})$ can be constructed by minimizing the convex functional

$$\Omega[V] = \frac{1}{\beta} \log \frac{\int d\mathbf{s}\, e^{-\beta[F(\mathbf{s})+V(\mathbf{s})]}}{\int d\mathbf{s}\, e^{-\beta F(\mathbf{s})}} + \int d\mathbf{s}\, p(\mathbf{s}) V(\mathbf{s}).$$

At the minimum the bias is such that the CVs are sampled according to a predefined target distribution $p(\mathbf{s})$ and furthermore the bias relates in a simple manner to the free energy surface as function of the CVs. There is considerable freedom in choosing the target distribution and the functional from of the bias potential. By combining the variational principle with an efficient stochastic optimization algorithm [2] we obtain a practical and flexible sampling method that allows us to effectively enhance the sampling and accurately determine the free energy surface.

Numerous numerical examples are presented which show that this approach is practical and useful. We furthermore discuss some innovative ideas that follow from the variational principle and allow to bias high-dimensional CV spaces.

[1] O. Valsson and M. Parrinello, *Phys. Rev. Lett.* 113 (2014) 090601.
[2] F. Bach and E. Moulines, *NIPS* 26 (2013) 773-781.

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